

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
États-Unis d'Amérique

in its capacity as elected Office

Date of mailing (day/month/year) 07 October 1998 (07.10.98)	
International application No. PCT/US98/02899	Applicant's or agent's file reference 2833.58
International filing date (day/month/year) 13 February 1998 (13.02.98)	Priority date (day/month/year) 13 February 1997 (13.02.97)
Applicant MAZESS, Richard, B. et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

14 September 1998 (14.09.98)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

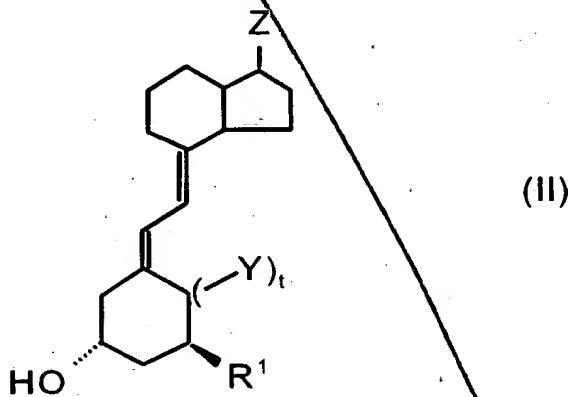
made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nicola Wolff
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

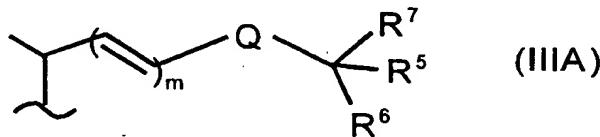
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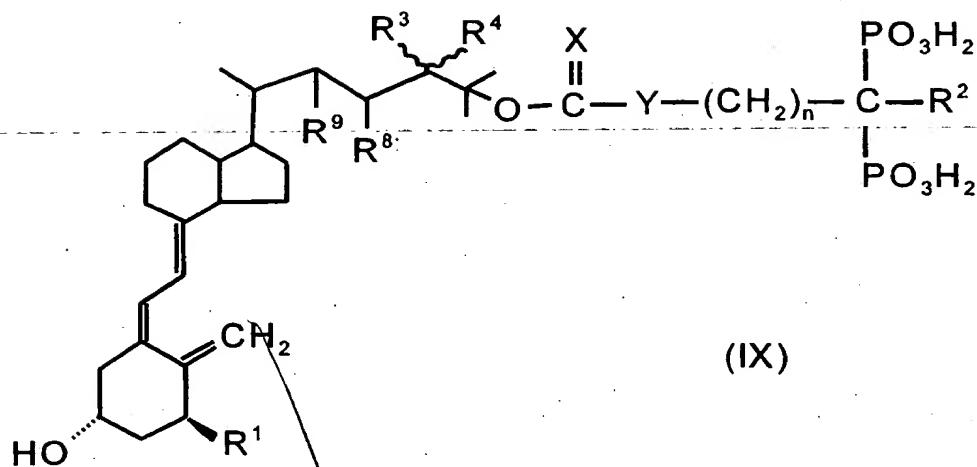
connector, via covalent bonding, hydrogen bonding, metallic bonding, van der Wall forces, ionic bonding, coulombic forces, hydrophobic or hydrophilic forces, adsorption or absorption, chelate type association, or any combination thereof. The terms "moiety" and "component" used in connection with vitamin D or D₃, or in connection with target molecule moiety or T, are meant to refer to vitamin D or target molecule in the conjugated forms disclosed herein, i.e., after association occurs. Association between the vitamin D analog and the target molecule may occur at any position on the vitamin D analog molecule depending on the functionality of the target molecule. For example, a bisphosphonate or amide may suitably link at positions on the vitamin D compound or vitamin D analog molecule having a hydroxyl group, such as at C-1, C-3, C-24, C-25.

Vitamin D compounds and analogs operable in the present invention are suitably represented by formula (II):



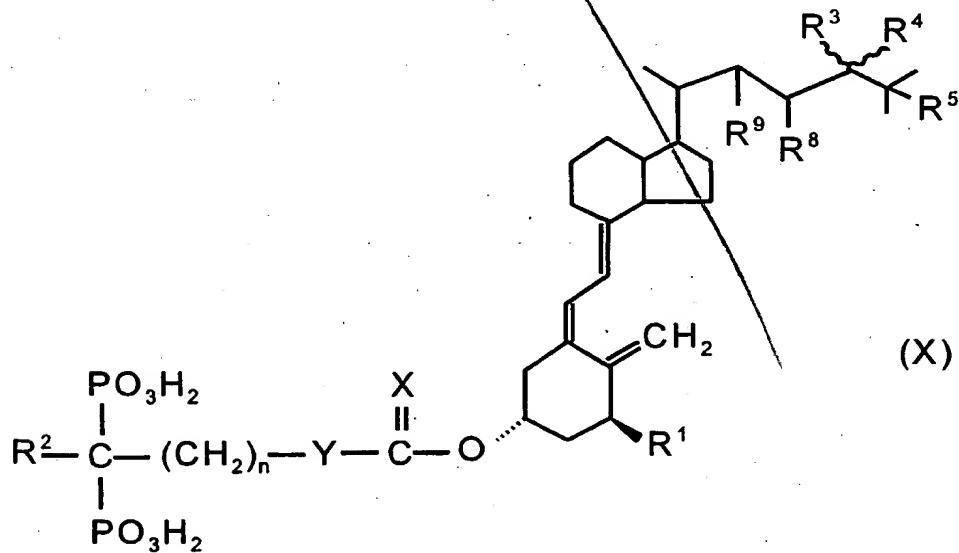
wherein R¹ is H or OH; Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₁ - C₁₈ hydrocarbon group; Y is a =CH₂ group; and t is 0 or 1, such that when t is 0, the compound of formula (II) is a 19-nor compound. Preferably, Z is a side chain represented by formula (IIIA):





wherein R¹ is H or OH; R² is H or OH; R³ is CH₃ or H; R⁴ is H or OH, X is O or S; Y is NH, O or NR wherein R is H or C₁-C₄ alkyl; n is an integer from 1 to 4; R⁸ and R⁹ are each H or taken together form a double bond between C-22 and C-23; and pharmaceutically acceptable salts thereof, i.e., the bisphosphonate is linked at the C-25 position of the vitamin D moiety.

Also provided are conjugates of formula (X):

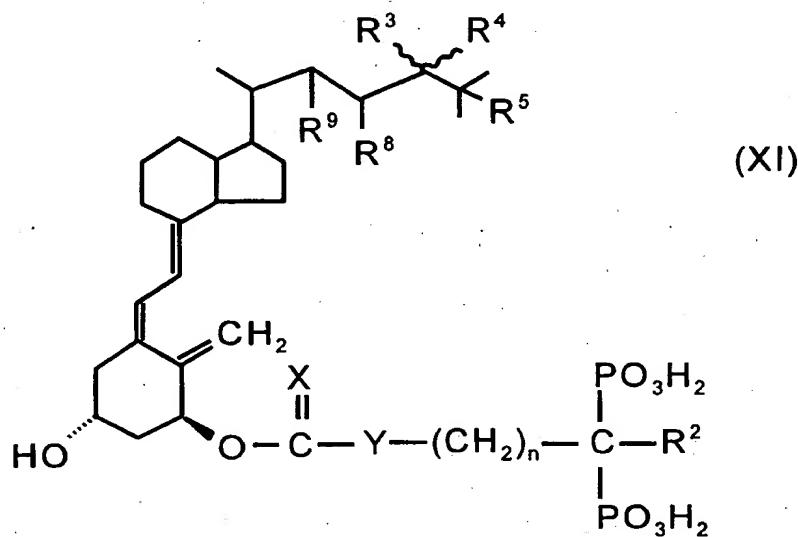


wherein R¹ is H or OH; R² is H or OH; R³ is CH₃ or H; R⁴ is H or OH, X is O or S; Y is NH, O or NR wherein R is H or C₁-C₄ alkyl; R⁵ is H or OH; n is an

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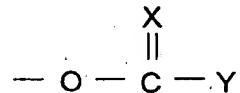
integer from 1 to 4; R⁸ and R⁹ are each H or taken together form a double bond between C-22 and C-23; and pharmaceutically acceptable salts thereof, i.e., the bisphosphonate is linked to the vitamin D moiety at C-3.

Also provided are conjugates of formula (XI):



5 wherein R² is H or OH; R³ is CH₃ or H; R⁴ is H or OH, X is O or S; Y is NH, O or NR wherein R is H or C₁-C₄ alkyl; R⁵ is H or OH, n is an integer from 1 to 4, R⁸ and R⁹ are each H or taken together form a double bond between C-22 and C-23; and pharmaceutically acceptable salts thereof, i.e., the bisphosphonate linkage is at C-1 of the vitamin D moiety.

10 It is noted that typically the linkage between the bisphosphonate moiety and the vitamin D moiety is through a hydroxyl on the vitamin D where the hydroxyl is converted to a



group and is linked to the amine or hydroxy group, i.e., Y, of the bisphosphonate to form a carbamate-type or carbonate-type linkage. X can be O or S. For example, a hydroxyl group may be contained in the vitamin D structure at C-1, C-3, C-24, C-25, and conjugation can be effected at any hydroxyl position but is suitably one of the above.

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PATENT COOPERATION TREATY

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REC'D	15 OCT 1999
WIPO	PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 17

Applicant's or agent's file reference MFF/FP5726708	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US98/02899	International filing date (day/month/year) 13/02/1998	Priority date (day/month/year) 13/02/1997
International Patent Classification (IPC) or national classification and IPC A61K47/48		
<p>Applicant BONE CARE INTERNATIONAL, INC. et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 14/09/1998	Date of completion of this report 18.05.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stoltner, A Telephone No. +49 89 2399 8408



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/02899

I. Basis of the report

1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

Description, pages:

**1-10,12-15,
18-35** as originally filed

11,16,17 as received on 07/01/1999 with letter of 04/01/1999

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

- 2. The amendments have resulted in the cancellation of:**

the description, pages:

the claims, Nos.:

the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c));

- #### 4 Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/02899

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims
	No:	Claims 1-40
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-40
Industrial applicability (IA)	Yes:	Claims 1-40 (except claims 23-27, 37 and 39 for some contracting states within the EPO)
	No:	Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/02899

ad section V:

- 1). The present application concerns a conjugate for the targeted therapeutic delivery of vitamin D compounds to specific tissue, said conjugate comprising a vitamin D compound bound to a target molecule moiety as set out in the present claim 1.
- 2). The following documents are considered relevant for the subject-matter of the present application:
 - D1, US-A-5 691 328, an intermediate document, discloses conjugates of vitamin D compounds with phosphoethanolamine with anti-tumor activity (cf. abstract) or for the treatment of osteomalacia (cf. col. 6, lines 37-47). As vitamin D compounds are bone therapeutic agents, it has also to be submitted that they are in some way "bone seeking" molecules, acting with affinity at a "tissue of interest" as pointed out in the application on page 8, last para. bridging with page 9, lines 1-7.
 - D2, US-A-5 232 836, refers to vitamin D derivatives covalently bound to immunogenic carrier proteins and antibodies (cf. abstract). In D2, the problem of delivering vitamin D conjugates to specific target tissues is also addressed (cf. col. 2, last para., col. 3, lines 58-64). Moreover, D2 also discloses connecting groups by which to couple the vitamin D compound to the carrier (cf. col. 27, lines 10-35). As set out in the application on page 9, lines 27-30, the vitamin D derivatives coupled to antibodies have the effect of targeting the vitamin D to, e.g., tumors. Moreover, in his letter of 12/4/99, the Applicant admits that vitamin D indeed has "traditional target tissues".
 - D3, WO-A-9 307 883, provides nucleosides linked to vitamin D by an aminoalkoxy or aminoalkylamino moiety (cf. claims 1-5). D3 encompasses the application of antisense agents for diagnostics and therapeutics where said antisense oligonucleotides are to be transported across cell membranes or "taken up by cells to express" activity. According to the Applicant, said cells have to be construed as pertaining to a "tissue of interest" (cells of interest).

**INTERNATIONAL PRELIMINARY
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- D4, J. Pharmacol. Exp. Ther., 237(3), 1986, pp. 837-840, J.M. Landowski et al., publishes the conjugation of vitamin D₃ compounds to glycopyranosides and the administration of said conjugates to vitamin D deficient rats maintained on a low calcium diet, whereby an increase of the intestinal calcium transport as well as the mobilization of the bone calcium was observed. As in the present application the term "target molecule" also encompasses molecules that "influences metabolism of the tissue of interest" (cf. page 9, lines 12-13), the raise of intestinal calcium transport implicitly also covers the metabolism of a tissue of interest (e.g. the metabolism of fatty acids).
- 3). In view of the above, it has to be noted that a conjugate or a composition as specified in claims 1 and 20 is known in the prior art. As appending to the main claims 1 and 20, the subject-matter of the subsequent claims 2-19 and 21-40 has also to be considered as anticipated by the prior art teaching.
- 4). For the assessment of the present claims 23-27, 37 and 39 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

ad section VI:

- 1). US-A-5 691 328, with a priority date of 27/8/96 and a publication date of 25/11/97;

ad section VIII:

- 1). The expression "..having an affinity for a tissue of interest" in claim 1 is unclear and includes no clear delimitation from the prior art. Moreover, this term can be construed as an attempt to define the invention by the result to be achieved, which gives no contribution to novelty or inventive step.

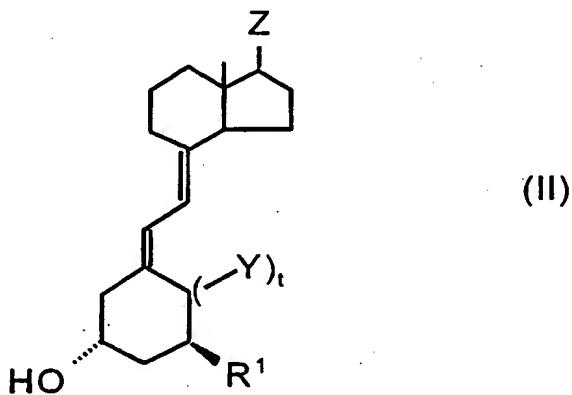
**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/02899

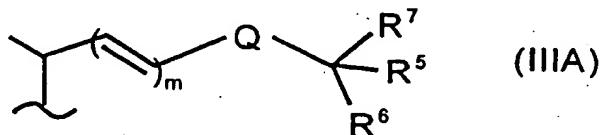
- 2). Incorporations made by reference (cf. page 20, line 16) are not accepted in the working practice of the EPO.

connector, via covalent bonding, hydrogen bonding, metallic bonding, van der Wall forces, ionic bonding, coulombic forces, hydrophobic or hydrophilic forces, adsorption or absorption, chelate type association, or any combination thereof. The terms "moiety" and "component" used in connection with vitamin D or D₃, or in connection with target molecule moiety or T, are meant to refer to vitamin D or target molecule in the conjugated forms disclosed herein, i.e., after association occurs. Association between the vitamin D analog and the target molecule may occur at any position on the vitamin D analog molecule depending on the functionality of the target molecule. For example, a bisphosphonate or amide may suitably link at positions on the vitamin D compound or vitamin D analog molecule having a hydroxyl group, such as at C-1, C-3, C-24, [▲]C-25.

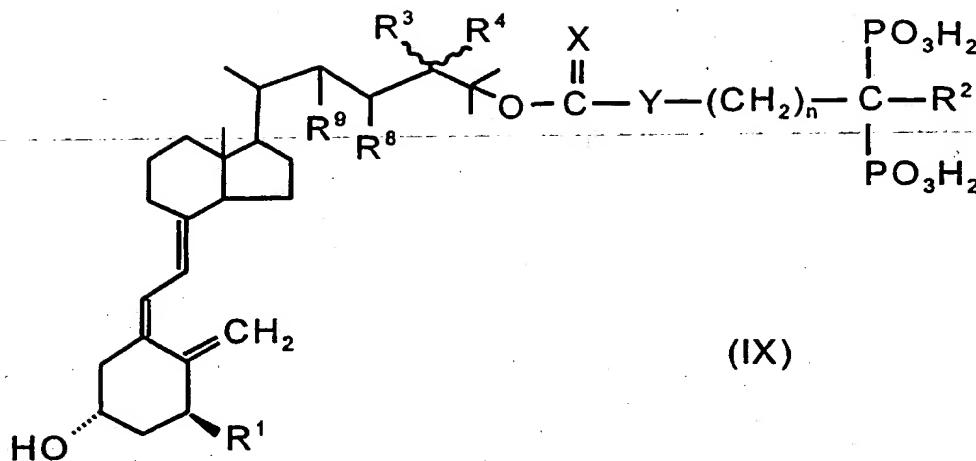
Vitamin D compounds and analogs operable in the present invention are suitably represented by formula (II):



wherein R¹ is H or OH; Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₁ - C₁₈ hydrocarbon group; Y is a =CH₂ group; and t is 0 or 1, such that when t is 0, the compound of formula (II) is a 19-nor compound. Preferably, Z is a side chain represented by formula (IIIA):

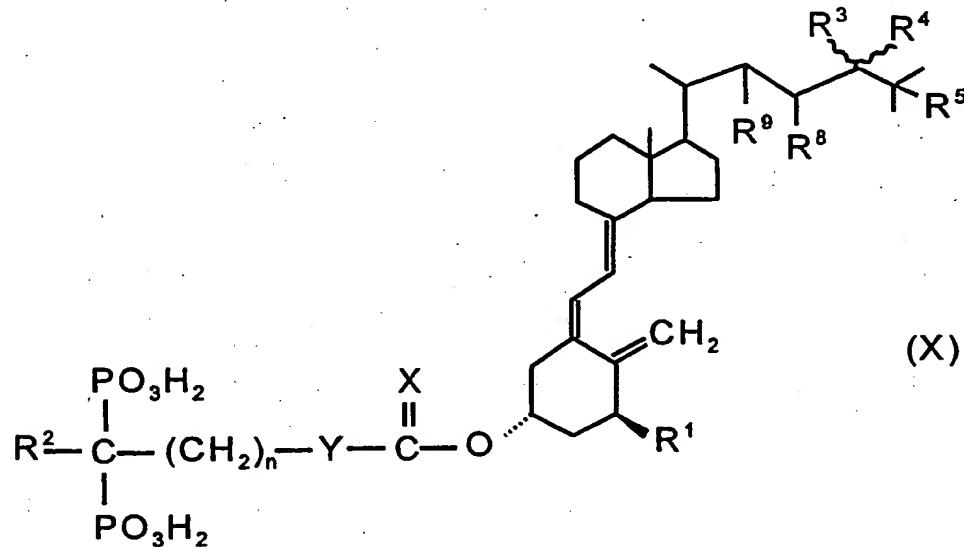


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wherein R¹ is H or OH; R² is H or OH; R³ is CH₃ or H; R⁴ is H or OH, X is O or S; Y is NH, O or NR wherein R is H or C₁-C₄ alkyl; n is an integer from 1 to 4; R⁸ and R⁹ are each H or taken together form a double bond between C-22 and C-23; and pharmaceutically acceptable salts thereof, i.e., the bisphosphonate is linked at the C-25 position of the vitamin D moiety.

Also provided are conjugates of formula (X):

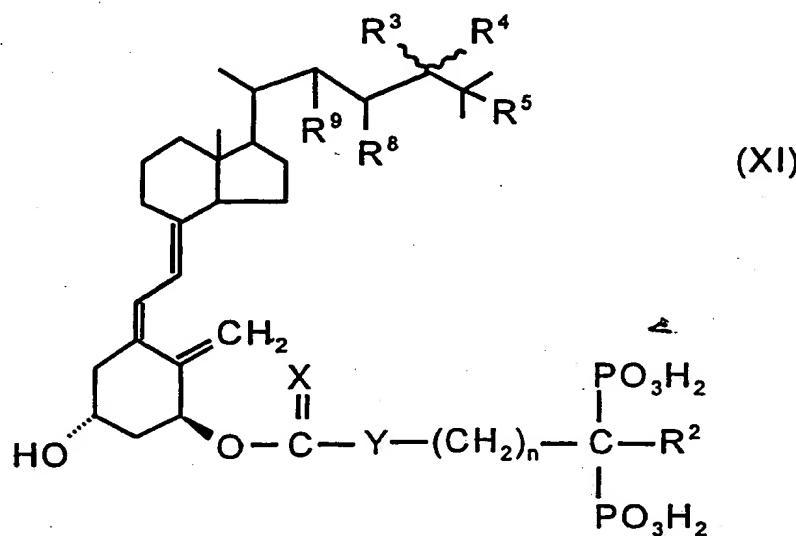


wherein R¹ is H or OH; R² is H or OH; R³ is CH₃ or H; R⁴ is H or OH, X is O or S; Y is NH, O or NR wherein R is H or C₁-C₄ alkyl; R⁵ is H or OH; n is an

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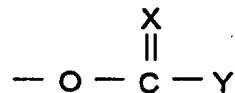
integer from 1 to 4; R⁸ and R⁹ are each H or taken together form a double bond between C-22 and C-23; and pharmaceutically acceptable salts thereof, i.e., the bisphosphonate is linked to the vitamin D moiety at C-3.

Also provided are conjugates of formula (XI):



5 wherein R² is H or OH; R³ is CH₃ or H; R⁴ is H or OH, X is O or S; Y is NH, O or NR wherein R is H or C₁-C₄ alkyl; R⁵ is H or OH, n is an integer from 1 to 4, R⁸ and R⁹ are each H or taken together form a double bond between C-22 and C-23; and pharmaceutically acceptable salts thereof, i.e., the bisphosphonate linkage is at C-1 of the vitamin D moiety.

10 It is noted that typically the linkage between the bisphosphonate moiety and the vitamin D moiety is through a hydroxyl on the vitamin D where the hydroxyl is converted to a



group and is linked to the amine or hydroxy group, i.e., Y, of the bisphosphonate to form a carbamate-type or carbonate-type linkage. X can be O or S. For example, a hydroxyl group may be contained in the vitamin D structure at C-1, C-3, C-24, C-25, and conjugation can be effected at any hydroxyl position but is suitably one of the above.

INT'L COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2833.58	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 02899	International filing date (day/month/year) 13/02/1998	(Earliest) Priority Date (day/month/year) 13/02/1997
Applicant BONE CARE INTERNATIONAL, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.
 It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title, the text is approved as submitted by the applicant
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 Figure No. _____
 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

Application No
PCT/US 98/02899

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K47/48 A61K31/59

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5 691 328 A (PETERSON ANDREW C ET AL) 25 November 1997 * cf. abstract, col. 6, lines 37-47, claims* ---	1-40
X	US 5 232 836 A (BOUILLOU ROGER ET AL) 3 August 1993 *cf. abstract, col. 2, last para., col. 27, lines 25-35, col. 29, lines 20-27*	1-40
X	WO 93 07883 A (ISIS PHARMACEUTICALS INC) 29 April 1993 *cf. claims 1-3* --- -/-	1-40

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search

28 May 1998

Date of mailing of the international search report

16/06/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stoltner, A

INTERNATIONAL SEARCH REPORT

Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LONDOWSKI J.M., KOST S.B. ET AL.: "Biological activity of the C-1, C-3, C-25, .beta.-D glucopyranosides of 1,25-dihydroxyvitamin D3" J. PHARMACOL. EXP. THER., vol. 237, no. 3, 1986, pages 837-840, XP002066239 * see the whole document* -----	1-40

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/02899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5691328 A	25-11-97	NONE	
US 5232836 A	03-08-93	FR 2631025 A EP 0341158 A ES 2045484 T JP 2262555 A US 5093519 A	10-11-89 08-11-89 16-01-94 25-10-90 03-03-92
WO 9307883 A	29-04-93	AU 2916292 A CA 2122030 A,C EP 0724447 A JP 6510791 T US 5578718 A	21-05-93 29-04-93 07-08-96 01-12-94 26-11-96